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REPORT NUMBER I

MECHANISMS OF RETINAL DAMAGE FROM CHRONIC LASER RADIATION

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AUG 20 1981
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Annual Report

1 September 1974 to 31 October 1975

T. Lawwill, M.D.; F. Sharp, B.S.E.E.; N. Speed; S. Crockett

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Contract Number DAMD 17 - 74 - C - 4026

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(6) Mechanisms of Retinal Damage from Chronic Laser Radiation

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(10) [redacted]/Lawwill, [redacted]; F./Sharp[redacted] N./Speed, [redacted]/Crockett

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SUMMARY:

This project is a study of the effect and the mechanisms of long-term exposure of the eye to laser radiation. The data is for four-hour, wide field exposures at levels below immediate damage threshold for monkey eyes. The report gives the thresholds for white light and for the 514.5 and 488 nm lines of the argon laser. Early data with the 457.9 nm line of the argon laser and with the 590 line of the Rhodamine 6G Dye Laser are also given.

This information is additive in the support of a hypothesis for mechanism of damage proposed and recorded in the final report of "Study of Ocular Effects of Chronic Exposure to Laser Radiation", DADA 17-68-8105.

FORWARD:

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care", as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences - National Research Council.

Monkeys were purchased from a reputable importer, quarantined and tested in his facility, quarantined again, and TB tested in our research animal facilities.

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We are in the third year of a definitive study to determine the mechanisms by which the eyes of primates may be damaged from chronic exposures to light. This study involves the establishment of thresholds of retinal damage produced by different wavelengths of light. In addition, by using several techniques for evaluation of the damage, we are attempting to define precisely the process by which such damage occurs. The main thrust of this study is to develop an understanding of the mechanism of damage so that thresholds for yet untested light sources may be predicted. The data which is collected should be useful in situations involving both laser illumination and white or colored light illumination from other sources.

The model which we have established involves monocular exposure of an experimental animal to a light source continuously for four hours. The light is presented to the eye in such a manner that a large area of the retina is evenly exposed. The intensity levels for exposure are below that necessary to raise the temperature of the retina. For periods of up to several weeks, we evaluate retinal damage in vivo using electroretinography as a monitor of the general state of retinal function, with ophthalmoscopy and fundus photography to record any gross morphological changes. Histopathology, combining both light and electron microscopy, is used as corroborative data. We plan to add fluorescein angiography as another technique for evaluation of retinal damage in vivo. At present, rhesus monkeys are used in the model because they offer the best comparison to man and are the least expensive in terms of loss of time and work secondary to unintentional death of the animals.

So far this project has produced unique data concerning damage thresholds for four-hour, wide-field exposures in primates. Our electron microscopy findings indicate a mechanism for damage in our model that is quite different from damage in similar exposure models in nocturnal animals. Consequently, this data is a key piece in the entire concept of chronic non-thermal light damage.

The objective of this study is to describe the mechanism by which non-thermal light damage occurs and to use the knowledge of the mechanism and the thresholds determined for present light sources to predict potential light damage from sources which have not yet been studied. So far this project has produced threshold data in rabbits for broadband white light and the 514.5 nm line of the argon laser and in monkeys for white light and the argon laser lines at 514.5 nm, 488.0 nm, and 457.9 nm.

During the immediate past year, several more exposures have been done at lower levels with broadband white light to complete the lower portion of that dose-response curve. Threshold has been fairly well determined for the 457.9 nm line and this is obviously a much lower threshold than the 514.5 and 488 nm lines. Preliminary data on a 590 nm line using the Rhodamine 6G Dye Laser has been collected. This early data for the 590 nm line shows that this wavelength is equal or slightly less than the 514.5 nm line in its ability to cause damage in a four-hour exposure.

METHODS:

I. Animals:

Rhesus monkeys weighing six to eight lbs. were used. The eyes are exposed to a wide-field source of light continuously for four hours.

II. Exposure:

The basic optical components are the same as those reported in previous communications. The light is presented in Maxwellian view with the focal point located just anterior to the crystalline lens. The beam entering the eye has a divergence of approximately 120° after coming to a focus at the pupil. The area of the retina illuminated by this apparatus is 5.8 cm^2 in the monkey. When the Coherent Radiation two-watt laser or the dye laser are used for illumination, the beam is expanded, and collimated, and inserted into the optical train using the same final lens for exposure. A Littrow prism is used to select the individual line of the argon laser when this is indicated by the protocol.

Exposure time is held constant at four hours, and the intensity of light varied in order to determine dose-response curves. Light intensity is measured with a Gamma Scientific 2020 spectroradiometer, calibrated with a standard source traceable to the National Bureau of Standards. Two methods have been used to determine the spacial distribution of the source. A large integrating detector is used to determine the total power entering the eye, and a much smaller detector is used to map the change in intensity from the center to the periphery of the beam. The spacial distribution is kept as uniform as possible by using only the

central portion of the collimated beam. In all cases, the intensity of light is calculated from the total power present at the cornea, divided by the total area of retina illuminated.

Anesthesia for exposure is necessary. In the monkey, a continuous drip of phenobarbital is utilized throughout the procedure. The pupils are dilated with tropicamide 1%, phenylephrine hydrochloride 10%, and atropine sulfate as necessary. The corneas are kept wet throughout the exposure with saline.

III. Electroretinography:

Electroretinograms are recorded binocularly by means of a standardized procedure developed in this laboratory. The monkeys are sedated with phencyclidine hydrochloride for ERG's.

Control data are collected for several weeks prior to exposure. After exposure, ERG's are recorded two to three times per week for several months. Post-exposure changes in the ERG are graded on a Ø to 4+ scale, according to the degree and persistence of the reduction of amplitude in the exposed eye.

IV. Ophthalmoscopy:

The fundi of the animals are examined by the investigator, using an indirect ophthalmoscope. Fundus photographs, as well as the investigator's impressions of the clinically visible damage, are taken one day, one week, and one month following exposure. Visible lesions are graded on a Ø to 4+ scale, according to the extent of edema and pigmentary changes in the fundus.

V. Pathology:

A. Light Microscopy: Sections of retina are prepared for light microscopy, using glutaraldehyde fixation, paraffin embedding, and hematoxylin and eosin staining. The appearance of the damage is graded on a Ø to 4+ scale, according to specific criteria previously reported.

B. Electron Microscopy: Sections of the retina are prepared for electron microscopy, using glutaraldehyde and osmium tetroxide fixation, epoxy resin embedding, and lead citrate and uranyl acetate staining. Sections are studied from the macular, paramacular and from peripheral areas of the retina. The electron microscopic appearance of the damage to the retina is graded on a Ø to 4+ scale, according to criteria previously presented.

RESULTS:

The first figure, marked Slide 11, shows the correlation coefficients and regression lines for the different techniques of examination after exposure. The measurements from the four techniques are taken separately, and not correlated until all measurements have been recorded. In this first figure, it can be seen that there is an excellent correlation between indirect ophthalmoscopy and electroretinography as well as between histology and electroretinography. The correlation is fair between electron microscopy findings and electroretinography. The correlation between indirect ophthalmoscopy and histology is not significant in the group of animals exposed to white light. (This may indicate that the particular mechanism of damage with white light may be different from that with the laser light). In the second figure, marked Slide 12, the correlations

between all methods of examination are excellent. The third figure, marked Slide 15, shows the data on white light exposures in monkeys from which the cumulative Gaussian curve was drawn (later figures). The next figure, marked Slide 16, is the data for laser exposures in monkeys at the 514.5 and 488 nm lines. This is the raw data from which the Gaussian curves were derived for later figures. The next figure, marked Slide 17, shows the individual means and standard deviations for data points with the white light and laser exposures. Though there appears to be a lower threshold for laser exposures, the result is marginally significant. The next figure, marked Figure 3, gives the cumulative Gaussian dose-response curve using the laser lines of 514.5 and 488 nm and broadband white light. Superimposed upon this, is the raw data for exposures at the 457.9 and 590 nm lines. The difference of almost one log unit between the 457.9 nm and the other lines is readily apparent.

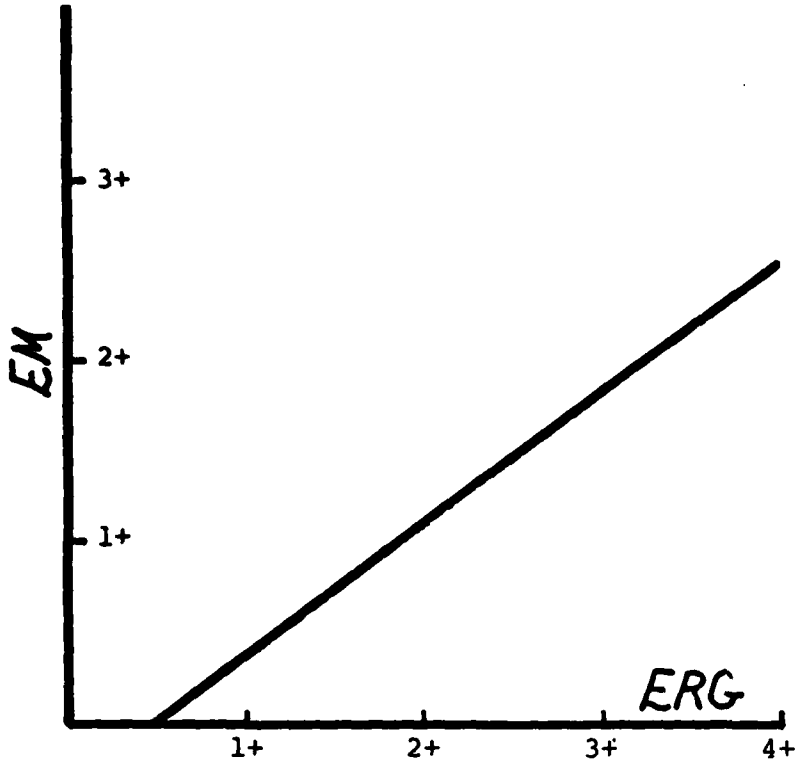
CONCLUSION:

It is obvious that mechanisms other than the specific absorption of light by unbleached visual pigment are operative in this damage mechanism. It is further obvious that the damage produced is secondary to the wavelength and intensity of the light and not to factors of coherence.

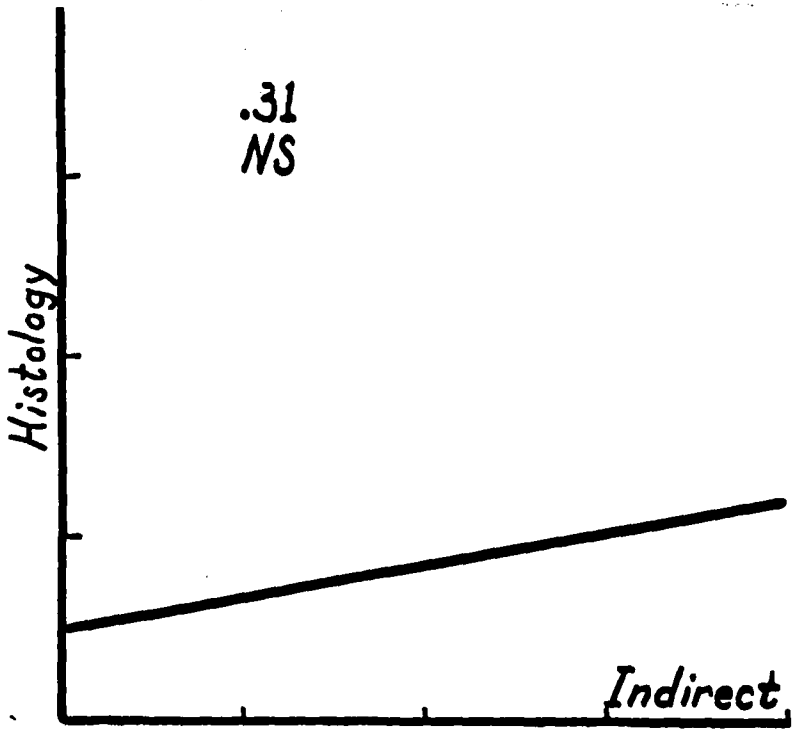
Further work delineating the mechanisms of damage in the area of the blue light will be necessary. This may require light sources different from those presently available in the laboratory. The poor repeatability of the indirect ophthalmoscopy examination requires the substitution of another technique in order to bring this examination technique up to the

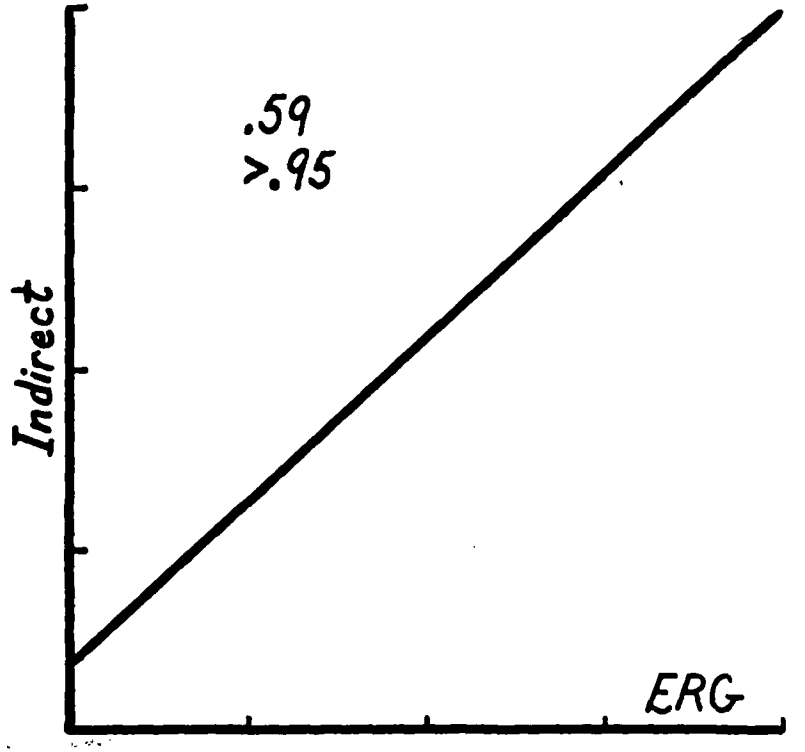
reliability of electroretinography. Fluorescein angiography is proposed for the next year for better reliability.

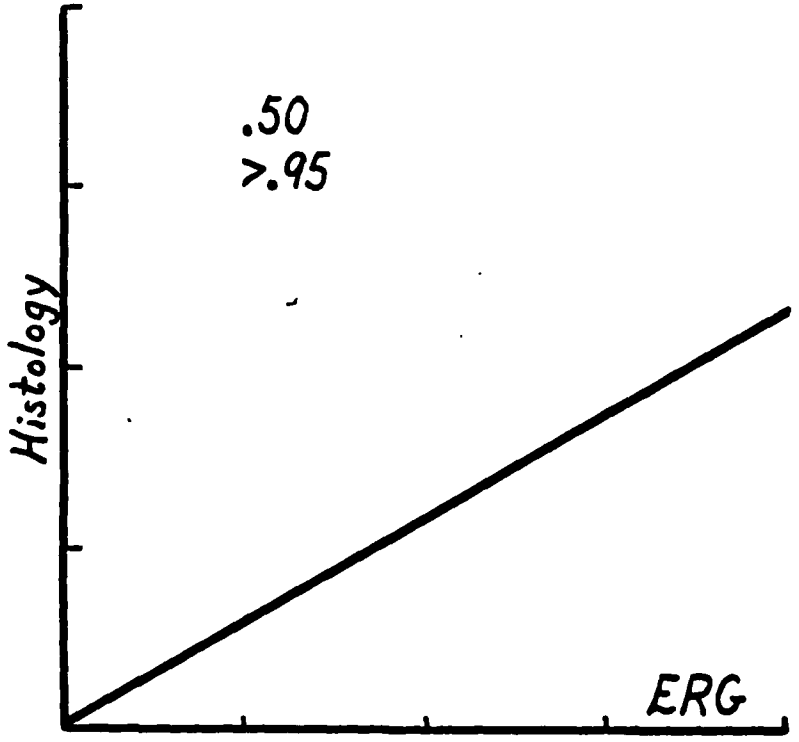
Slide 11



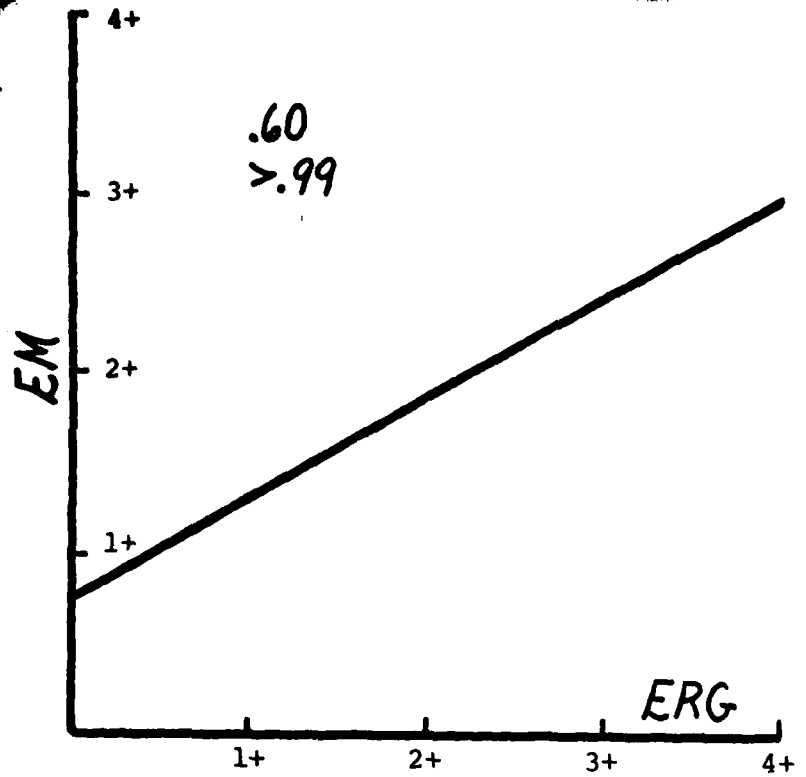
White Light



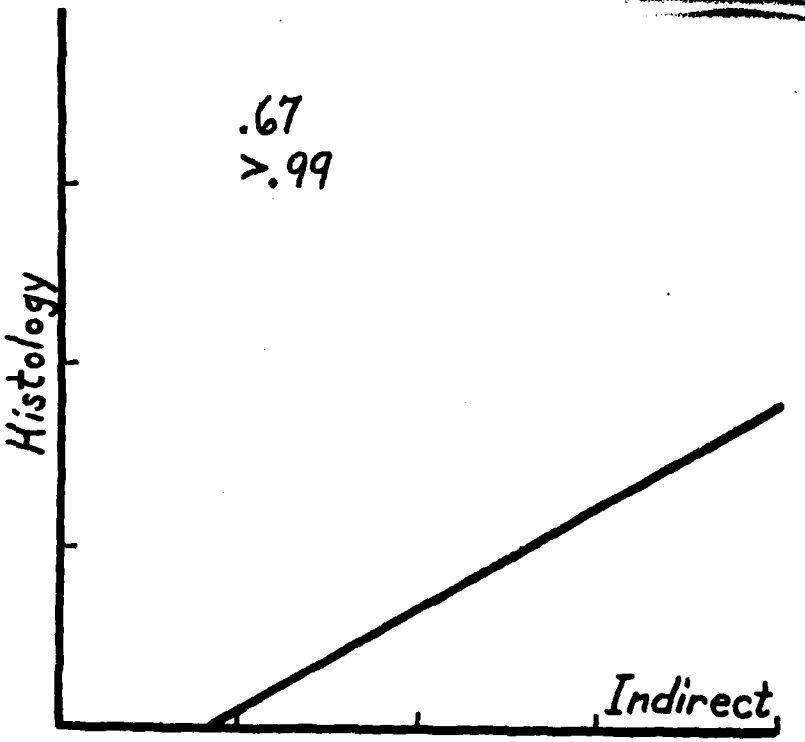


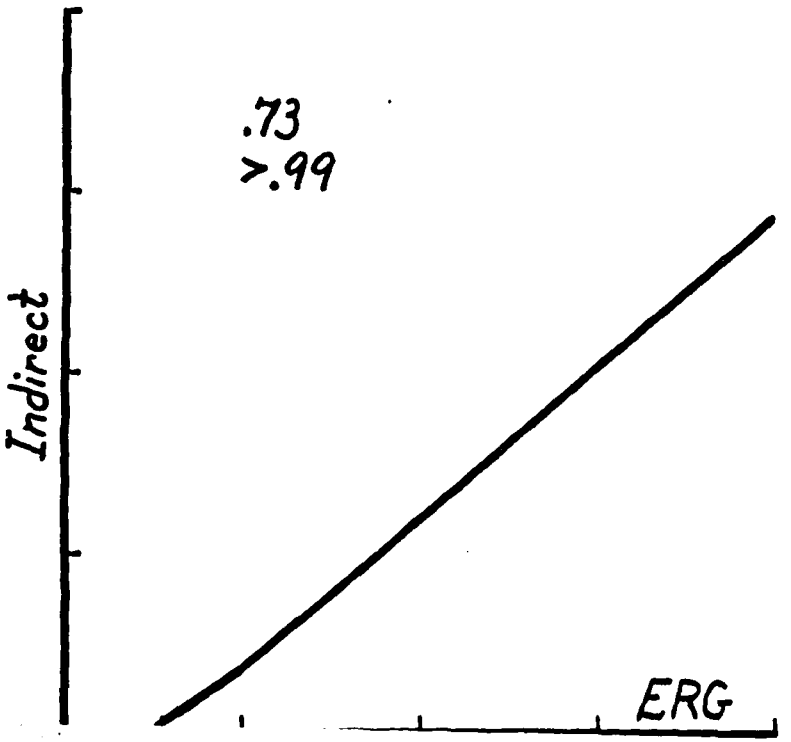


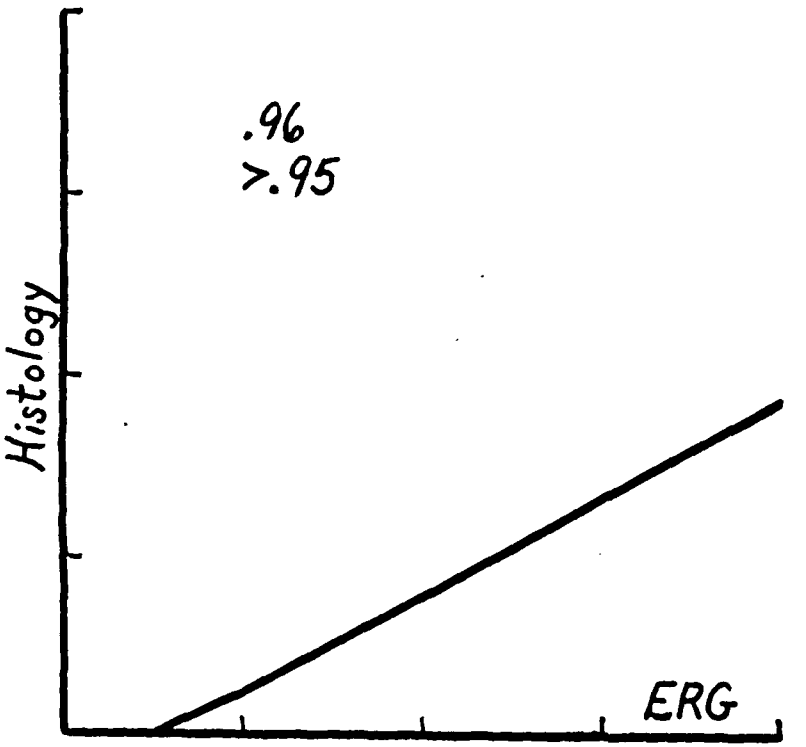
Slide 12



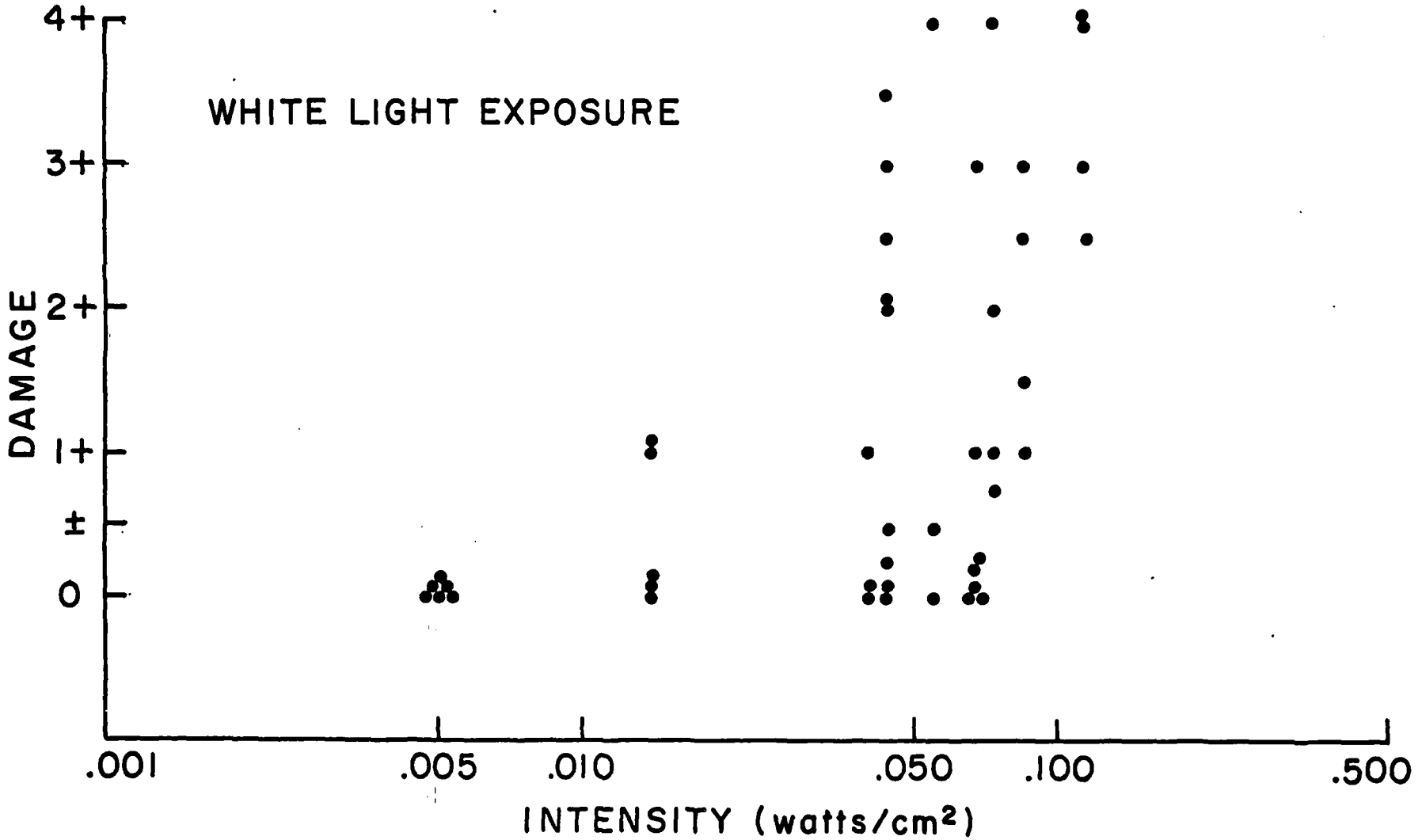
Laser



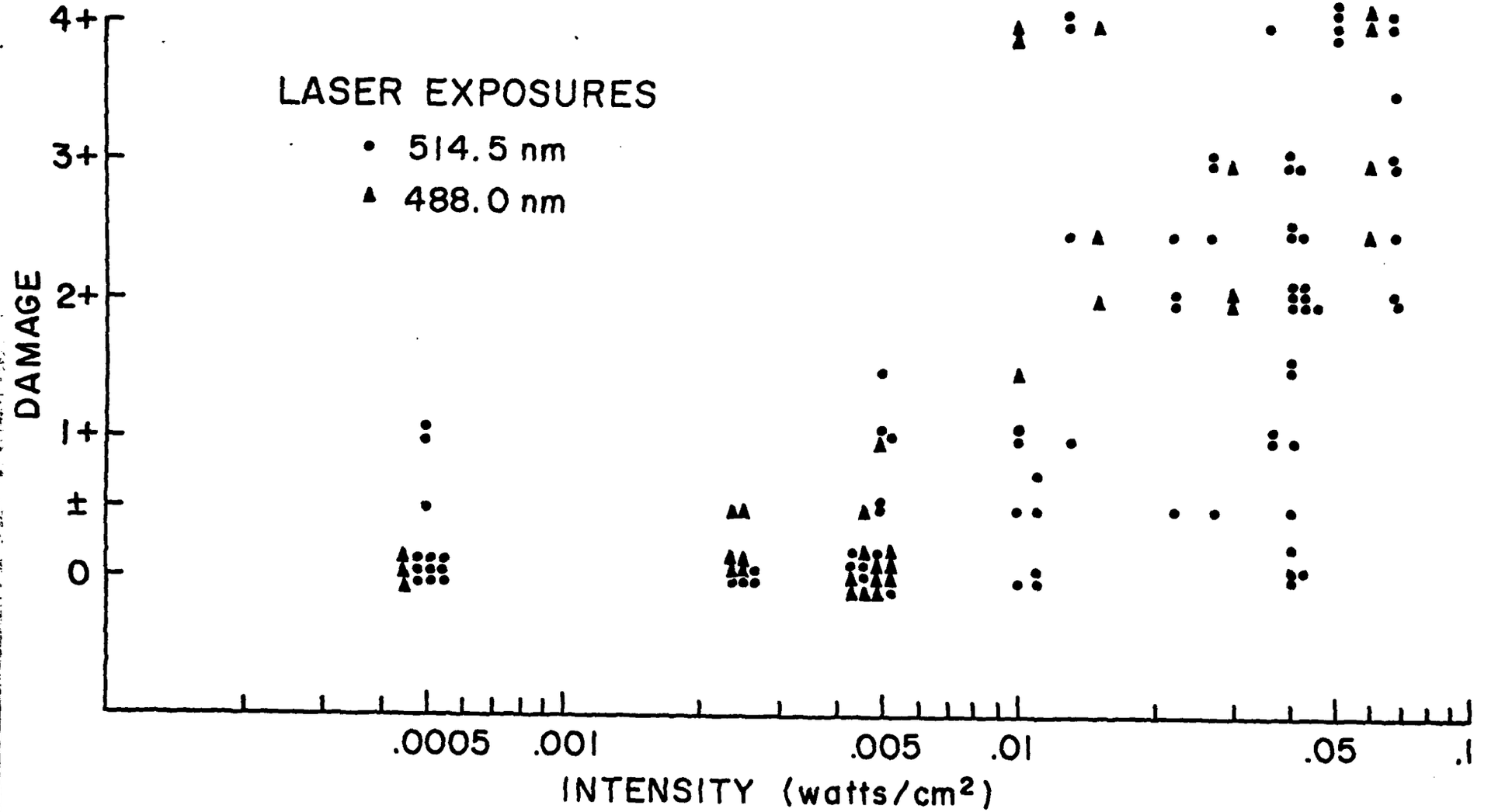




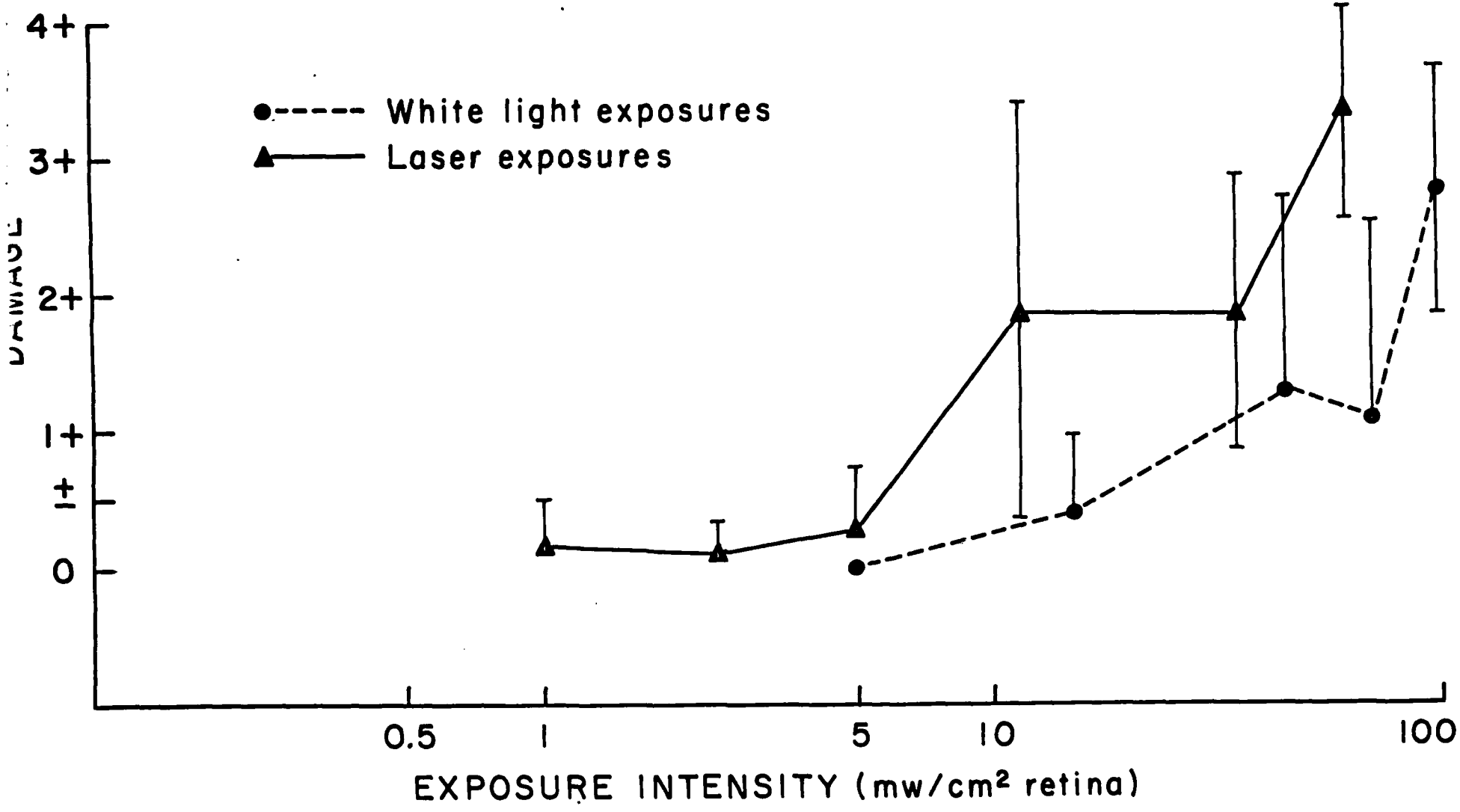
Slide 15


WHITE LIGHT EXPOSURE
DAMAGE
4+
3+
2+
1+
±
0
.001
.005
.010
.050
.100
.500
INTENSITY (watts/cm²)

Slide 16


LASER EXPOSURES
• 514.5 nm
▲ 488.0 nm
DAMAGE
4+
3+
2+
1+
±
0
.0005
.001
.005
.01
.05
.1
INTENSITY (watts/cm²)

Slide 17


4+
3+
2+
1+
±
0
White light exposures
Laser exposures
0.5
1
5
10
100
EXPOSURE INTENSITY (mw/cm² retina)

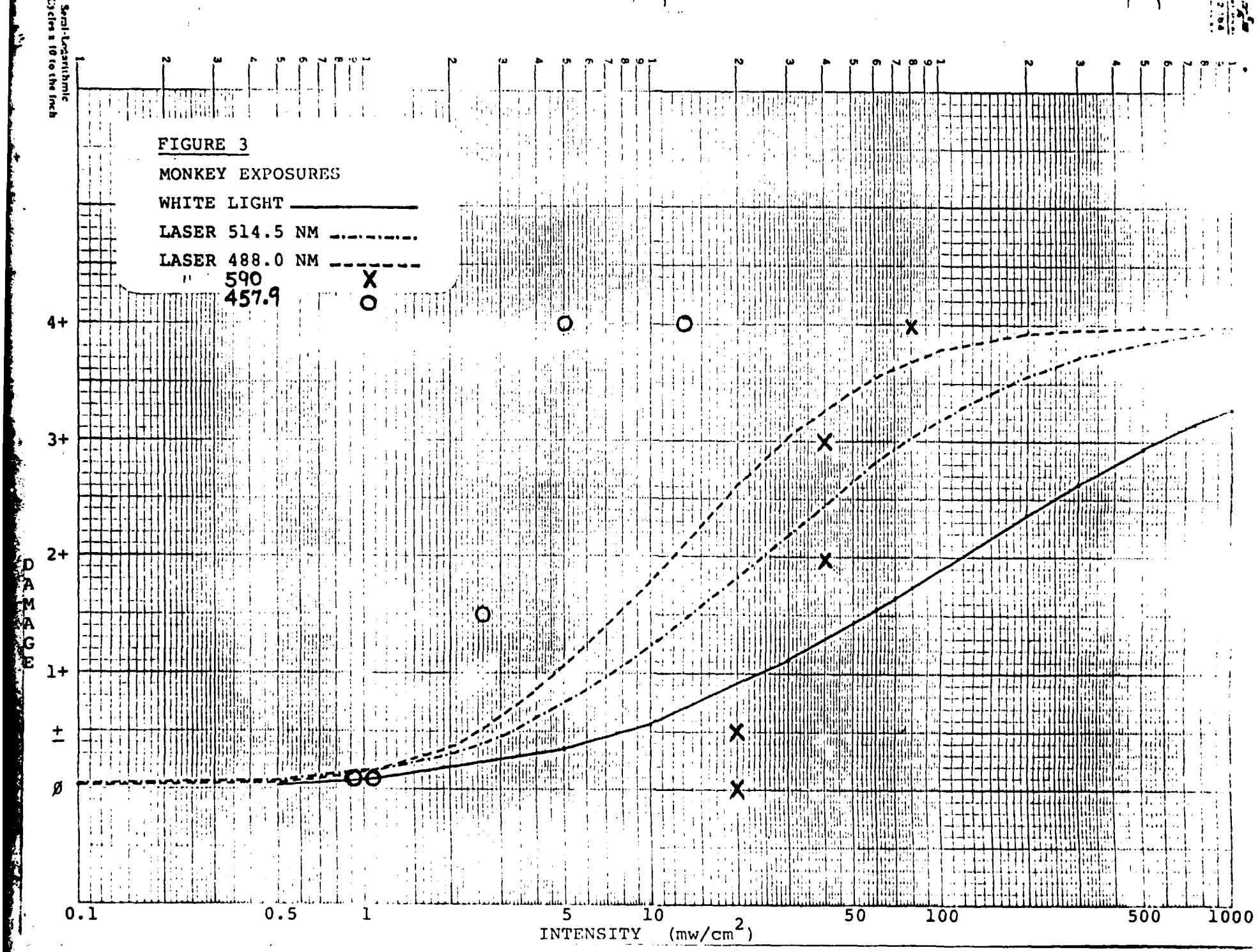
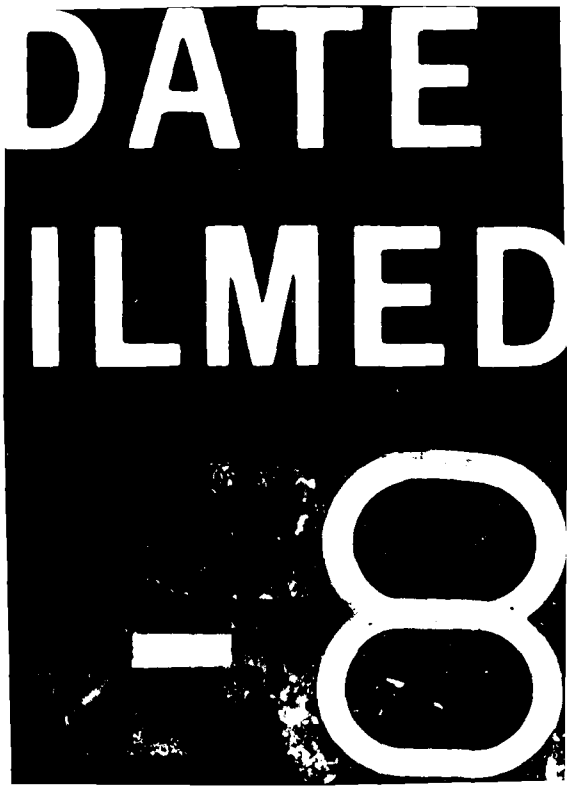


FIGURE 3
MONKEY EXPOSURES
WHITE LIGHT
LASER 514.5 NM
LASER 488.0 NM
" 590
457.9
4+
3+
2+
1+
+1
ø
DAMAGE
0.1
0.5
1
5
10
50
100
500
1000
INTENSITY (mw/cm2)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